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Regional Left Ventricular Asynchrony and Impaired Global Left Ventricular Filling in Hypertrophic Cardiomyopathy: Effect of Verapamil

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Left ventricular relaxation and filling are impaired in many patients with hypertrophic cardiomyopathy. To investigate the influence of regional heterogeneity on these global abnormalities, 48 patients with hypertrophic cardiomyopathy and sinus rhythm were studied by radionuclide angiography before and after 1 to 2 weeks of verapamil therapy (320 to 640 mg/day, median 480). Left ventricular regional function was assessed by subdividing the ventricular region of interest into 20 sectors and into four quadrants from which regional time-activity curves were derived. Diastolic asynchrony was measured as the regional variation in timing between minimal volume and peak filling rate, and heterogeneity in the magnitude of rapid diastolic filling was measured as the regional variation in percent contribution of atrial systole to end-diastolic volume.

Compared with 28 normal subjects, the patients with hypertrophic cardiomyopathy had greater regional variation in both timing (35 ± 24 versus 12 ± 6 ms, $p < 0.001$) and magnitude (10 ± 6 versus 7 ± 4%, $p < 0.02$) of rapid filling. Verapamil reduced the regional variation in timing (to 21 ± 16 ms, $p < 0.001$) and magnitude (to 7 ± 3%, $p < 0.001$) of rapid filling. These regional changes, indicating more uniform regional diastolic performance after verapamil, were associated with improved global diastolic filling: global rapid filling increased in both rate and magnitude and time to peak filling rate decreased. These findings indicate that the beneficial effect of verapamil on left ventricular diastolic function in hypertrophic cardiomyopathy may be mediated by reduction in regional asynchrony.

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Left ventricular diastolic function is impaired in many patients with hypertrophic cardiomyopathy (1–6). Reduced rate and magnitude of left ventricular rapid diastolic filling in this disease reflect not only decreased left ventricular distensibility (7–11) arising from hypertrophy, fibrosis or cellular disorganization, but also disturbances in active left ventricular relaxation (1–4,12,13). Numerous studies (14–24) of ischemic heart disease have demonstrated that global left ventricular relaxation may be prolonged or incomplete in the setting of nonuniform regional left ventricular function arising from segmental ischemia or fibrosis. However, the relation between spatial and temporal nonuniformity and impaired global ventricular diastolic filling has not been studied extensively in hypertrophic cardiomyopathy, and the potential for reversal of regional heterogeneity during medical therapy in this disease has not been addressed.

In our study, we evaluated regional left ventricular asynchrony and its relation to global left ventricular filling in patients with hypertrophic cardiomyopathy using radionuclide angiography. Because oral verapamil enhances left ventricular relaxation and filling in such patients (5,6,25–27), we also studied the effect of verapamil on regional left ventricular asynchrony in relation to changes in global ventricular diastolic filling.

Methods

Patient selection. We studied 48 patients with hypertrophic cardiomyopathy by radionuclide angiography before and after they underwent 1 to 2 weeks of verapamil therapy. Patients ranged in age from 21 to 69 years (mean 43); there were 29 men and 19 women. In each patient, the diagnosis of hypertrophic cardiomyopathy was based on M-mode or two-dimensional echocardiographic confirmation of a hypertrophied, nondilated left ventricle in the absence of an-

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other cardiac or systemic disease capable of causing myocardial hypertrophy (28). Cardiac catheterization in 46 patients demonstrated a rest subaortic pressure gradient of ≥30 mm Hg in 18 patients (37%), a provocable gradient during the Valsalva maneuver, amyl nitrite inhalation or intravenous isoproterenol infusion in 18 (37%) and no rest or provocable gradient in 10 (21%). The two patients who were not catheterized manifested marked systolic anterior motion of the anterior mitral valve leaflet on echocardiography, compatible with a rest outflow tract gradient (29). All patients were limited by moderate to severe symptoms of angina, exertional dyspnea, orthopnea or paroxysmal nocturnal dyspnea (New York Heart Association functional class III to IV). All had normal sinus rhythm. Concomitant coronary artery disease was excluded in 33 patients by coronary arteriography; 31 of these patients had completely normal arteriograms and 2 had only mild coronary atherosclerosis (<50% reduction in luminal diameter). Of the 15 patients who did not undergo coronary arteriography, 13 were <40 years of age (6 were ≤30); the other 2 patients were <45 years and did not report angina pectoris. Forty-three of the 48 patients were included in a previous study demonstrating the relation between improved left ventricular filling during verapamil therapy and increased exercise tolerance (27).

Patients were included in this study under guidelines of protocols 77-H-156 and 80-H-65 approved by the Clinical Research Subpanel of the National Heart, Lung, and Blood Institute on September 2, 1977 and June 23, 1980, respectively. All patients gave written informed consent. The radiation exposure from a single radionuclide angiogram is estimated to be 0.357 rad (total body dose).

Verapamil administration. Radionuclide angiography was performed at least 48 hours after cessation of propranolol and all other cardiac medications. No patient had been receiving other beta-adrenergic blocking agents before entering this study, and no patient had been treated previously with verapamil. After baseline studies were complete, verapamil was administered orally, beginning at 240 to 320 mg/day in divided doses. The dose was increased gradually every 36 to 48 hours as tolerated, to a target dose of 480 mg/day. The final dosage was determined by the clinical response of each patient and was limited in some patients because of atrioventricular (AV) dissociation, Mobitz type I second degree AV block or systemic hypotension. The final daily verapamil dose was 320 mg in 9 patients, 360 mg in 11, 480 mg in 26 and 640 mg in 2. Radionuclide angiography was repeated after each patient received what was considered to be the optimal dose for at least 36 hours.

Gated Blood Pool Cardiac Scintigraphy

Data acquisition. Radionuclide angiography was performed at rest with patients in the supine position using red blood cells labeled in vivo with 15 to 20 mCi of technetium-99m and a conventional Anger camera equipped with a high sensitivity, parallel-hole collimator oriented in a modified left anterior oblique position. A total of 7.5 to 10.5 million counts was acquired for each study. High temporal resolution (10 to 20 ms/frame) cardiac image sequences were constructed by computer-based electrocardiographic (ECG) gating, with the use of list-mode data acquisition with exclusion of extrasystolic and postextrasystolic cycles and combined forward and reverse gating from the R wave (5,30). Left ventricular time-activity curves, representing relative changes in left ventricular volume during the average cardiac cycle, were generated from the cardiac image sequence after background correction with a fixed left ventricular region of interest, which was constructed manually to conform to the borders of the left ventricle as identified from the end-diastolic image, the stroke volume image and the amplitude image. This latter functional image was created by approximating each single-pixel time-activity curve with the first harmonic of its temporal Fourier expansion (31). After the region of interest was identified in this manner, the time-activity curve was constructed from the raw image sequence without spatial or temporal smoothing processes.

Analysis of global left ventricular function. Indexes of global left ventricular function were derived by computer analysis of the background-corrected time-activity curve. Ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts. Peak left ventricular ejection and filling rates were determined by fitting third order polynomial functions to the systolic ejection and rapid diastolic filling portions of the time-activity curve by a least squares technique (5). The time of occurrence of the peak ejection or peak filling rate was obtained by setting the second derivative of the polynomial function to zero. Time to peak ejection rate was measured from the R wave and time to peak filling rate was measured relative to end-systole (minimal volume on the time-activity curve). Both peak ejection rate and peak filling rate were computed in left ventricular counts/s, normalized for the number of counts at end-diastole and expressed as fractional end-diastolic counts (or end-diastolic volume)/s (EDV/s). When normalized for end-diastolic volume, both peak ejection rate and peak filling rate are influenced inversely by the magnitude of end-diastolic volume and directly by the magnitude of the ejection fraction (32,33). Because patients with hypertrophic cardiomyopathy as a group have reduced end-diastolic volume and a supranormal ejection fraction, comparison of the filling rate data between these patients and normal subjects is difficult. To minimize this effect, we also analyzed peak filling rate using two additional normalization methods: peak filling rate was expressed relative to left ventricular stroke volume (SV/s) and as the ratio of peak filling rate to peak ejection rate (22,34). These two latter methods have the additional advantage of being background independent.

We also determined the contribution of atrial systole to

JACC Vol. 9, No. 5
May 1987:1108–16

left ventricular filling volume and end-diastolic volume in 44 of the 48 patients. This additional analysis could not be performed in four patients because a definite diastasis interval separating rapid diastolic filling from atrial systole was not evident on the time-activity curve, and hence the contribution of atrial systole could not be differentiated from that of rapid filling. In the 44 patients in whom diastasis was observed, the onset of atrial systole was determined as previously described (6). The total duration of the PR interval (onset of P wave to onset of QRS complex) plus the interval from the QRS onset to the instant of R wave gating (peak negative R to S transition) was measured to the nearest 20 ms from an ECG rhythm strip obtained during the radionuclide data acquisition. This sum was subtracted from the cardiac cycle length to indicate the point on the time-activity curve representing the onset of electrical atrial activation; 40 ms was added to this value to account for atrial electromechanical delay, and this new point on the curve was chosen as the onset of mechanical atrial systole (6). Relative left ventricular filling during atrial systole was then computed as a percent of total left ventricular stroke volume and left ventricular end-diastolic volume. A three point (that is, 60 ms) average was performed about the point on the curve selected as the onset of atrial systole to minimize the influence of random noise.

In addition to these indexes describing global left ventricular function, we also analyzed relative regional left ventricular asynchrony by sector analysis (22,35). This was accomplished by dividing the left ventricular region of interest first into 20 sectors and then into four quadrants.

Sector analysis. The left ventricular region of interest was divided into 20 sectors of equal arc (18°), each emanating from the end-diastolic left ventricular center of gravity. The inner one-third of each sector was then excluded, yielding annular sectors constituting the outer two-thirds of the left ventricle (35). From these fixed regions, sectorial time-activity curves were generated, representing the change in counts within each sector during the average cardiac cycle. From these data, we computed an index of regional systolic asynchrony and an index of regional homogeneity in the extent of rapid diastolic filling.

The index of regional systolic asynchrony was obtained by describing each sector time-activity curve by a two-harmonic Fourier expansion. The nadir of this curve was used to approximate the time to minimal volume (measured from the R wave) of each sector. The variation in time to minimal volume among sectors was assessed quantitatively as the standard deviation about the mean value for the 20 sectors (22).

The index of regional homogeneity of rapid filling was determined as the variation among sectors in relative filling during atrial systole in the 44 patients in whom it was possible to assess the contribution of atrial systole in the global time-activity curve. For these regional measurements, the volume filled during atrial systole for each sector was computed as a percent of the end-diastolic volume of that sector, using the same method used to compute the contribution of atrial systole to global filling volume. The regional variation in percent filling during atrial systole was then assessed, as with the time to minimal volume data, by computing the standard deviation about the mean value of the 20 sectors. Because there is an excellent inverse relation between the percent of left ventricular volume filled during atrial systole and the percent filled during the rapid filling period (6), we used the regional variation in contribution of atrial systole to reflect regional heterogeneity in the magnitude of rapid diastolic filling.

Quadrant analysis. Computation of more specific temporal indexes from the 20 sector time-activity curves, such as time to peak ejection rate or time to peak filling rate, was not possible because of the limited precision of measurement caused by counting fluctations in each sector curve, resulting in large errors in the measurement of these specific intervals. To improve the precision and reduce the errors in these specific regional temporal measurements, we created quadrants by combining the 20 sectors into four quadrants of 5 sectors each (22). Regional time-activity curves were then generated from each quadrant, which were then fit to a Fourier expansion with three harmonics (36). From the fitted curve, the time to peak ejection rate, time to minimal volume and time to peak filling rate were computed. Time to peak ejection rate and time to minimal volume were measured from the R wave, whereas time to peak filling rate, as in the global volume curve, was expressed relative to each quadrant's time to minimal volume. From each of the fitted quadrant curves, we also computed the extent of left ventricular filling during atrial systole as a percent of end-diastolic volume. To assess the regional variation in each of these variables, the absolute value of the difference between the global value and the value for each of the four quadrants was calculated, and these four differences were then averaged (22).

Reproducibility of regional measurements. Reproducibility of the regional data obtained from sector and quadrant analyses were determined in 25 patients with hypertrophic cardiomyopathy. In these patients, two radionuclide angiographic data acquisitions were obtained at rest after withdrawal from all cardioactive medicines. From these duplicate studies, confidence limits for reproducibility of each variable were determined as the mean difference plus 2 SD. The reproducibility limit for the regional variation measurements by sector analysis was 22 ms for time to minimal volume and 8% for regional filling during atrial systole. These limits for regional variation by quadrant analysis were 8 ms for time to peak ejection rate, 11 ms for time to minimal volume, 12 ms for time to peak filling rate and 6% for regional filling during atrial systole. Reproducibility limits for measurements of global left ventricular

function in these 25 patients have been reported previously (6).

Normal data. The normal values for indexes of global left ventricular function and regional left ventricular asynchrony have been presented previously (22) in 28 asymptomatic normal subjects without any evidence of cardiovascular disease on the basis of history, blood pressure, physical examination, echocardiogram and chest X-ray film. These subjects ranged in age from 31 to 60 years (mean 46) and were used again in our study as a control group. The data in these subjects were obtained during the same time period as were the data in the hypertrophic cardiomyopathy patients and were analyzed by the same technical staff. To complete the normal data base for our investigation, we analyzed the contribution of atrial systole to left ventricular filling volume for the global, sector and quadrant time-activity curves in 25 of the 28 subjects. Three subjects were excluded from this particular analysis because a definite diastasis interval separating rapid diastolic filling from atrial systole was not evident. The regional variation in magnitude of left ventricular filling during atrial systole was then computed as in the patients with hypertrophic cardiomyopathy.

Echocardiography

The radionuclide angiographic data pertaining to regional left ventricular function were compared with regional morphologic data obtained by two-dimensional echocardiography in 39 of the 48 patients. A Varian (V-3000 or V-3400) real-time, phased array, ultrasound sector scanner with a hand-held 2.25 MHz transducer, or an Advanced Technology Laboratory (ATL) Mark 500 mechanical sector scanner (84°) with a 3 MHz transducer was used to perform the echocardiographic studies. Images were recorded on either a 0.5 inch (1.27 cm) (Sanyo) cassette videotape or 1 inch (2.54 cm) (Sony) reel to reel videotape for subsequent review in real-time, slow motion or stop action mode. Two-dimensional echocardiographic examination included images obtained in the parasternal long-axis and multiple short-axis views, as well as apical two and four chamber views using standard transducer positions (37).

The technical quality of the echocardiographic studies permitted reliable assessment of the extent and distribution of left ventricular hypertrophy in 33 of the 39 patients. For purposes of our study, the presence and magnitude of hypertrophy involving the basal and apical portions of the ventricular septum and posterolateral free wall and the left ventricular apex were assessed by two-dimensional echocardiography (38) and were compared with data obtained from corresponding regions of the left ventricle by radionuclide angiography. Echocardiographic analysis was performed without knowledge of the radionuclide angiographic results.

Statistical methods. Comparison between normal subjects and the patients with hypertrophic cardiomyopathy was performed with the *t* test for unpaired data. Linear regression analysis was used to test the relation between the regional indexes of asynchrony and global indexes of diastolic filling, and between the regional indexes of asynchrony and the magnitude of the left ventricular outflow gradient measured at catheterization. Changes from before to after verapamil were analyzed with the *t* test for paired data.

Results

Global left ventricular function. Under control conditions, both left ventricular ejection fraction and peak left ventricular ejection rate were elevated in the patients with hypertrophic cardiomyopathy compared with the normal subjects (Table 1). Time to minimal volume was prolonged in the patients with hypertrophic cardiomyopathy, reflecting prolongation of systolic ejection in patients with an outflow tract gradient (13,39); time to minimal volume in the 10 patients without outflow obstruction (327 ± 26 ms) was significantly shorter than that of either the 18 patients with rest outflow obstruction (389 ± 35 ms, $p < 0.001$) or the 18 patients with provocable obstruction (370 ± 46 ms, $p < 0.01$).

Left ventricular rapid diastolic filling was impaired in the patients with hypertrophic cardiomyopathy. Although the peak rate of left ventricular filling was not different from that of the normal subjects when normalized to end-diastolic volume (Table 1), it was significantly less than normal when normalized to left ventricular stroke volume or expressed as the ratio of peak filling to peak ejection rate (thereby minimizing the influence of reduced end-diastolic volume or supranormal ejection fraction [34]). Moreover, time to peak filling rate was prolonged and the contribution of atrial systole to left ventricular filling volume was increased compared with normal. None of the diastolic filling variables differed among patients with regard to the presence or severity of outflow tract gradients.

Regional left ventricular asynchrony. The global abnormalities of diastolic filling in patients with hypertrophic cardiomyopathy were associated with significant systolic and diastolic asynchrony: the regional variation in both time to minimal volume and time to peak filling rate was greater than normal (Table 1, Fig. 1). The regional variation in time to peak filling rate (the index of diastolic asynchrony) correlated with global peak filling rate ($r = 0.43$, $p < 0.01$). No such correlation was observed between indexes of systolic asynchrony and global filling variables. No index of regional asynchrony correlated with the presence or severity of an outflow tract gradient or with the prolongation of global time to minimal volume.

Regional variation in contribution of atrial systole. The diastolic asynchrony in the patients with hypertrophic

Table 1. Variables Describing Global and Regional Left Ventricular Function

	Normal Subjects (n = 28)	Patients With HCM (n = 48)		
		Control	Verapamil	p Value
Heart rate (beats/min)	71 ± 12	70 ± 11	67 ± 9†	<0.01
Systemic blood pressure (mm Hg)				
Systolic	122 ± 11	116 ± 18	114 ± 14‡	NS
Diastolic	76 ± 8	67 ± 12	68 ± 11	NS
Global LV systolic function				
LV ejection fraction (%)	56 ± 7	75 ± 10§	75 ± 9§	NS
Peak LV ejection rate (EDV/s)	3.1 ± 0.6	3.9 ± 0.7§	3.9 ± 0.6§	NS
Time to minimal LV volume (ms)	341 ± 31	367 ± 43‡	360 ± 30†	NS
Global LV diastolic filling				
Peak LV filling rate				
EDV/s	3.3 ± 0.6	3.3 ± 1.1	4.3 ± 1.3§	<0.001
SV/s	5.7 ± 1.1	4.5 ± 1.4§	5.8 ± 1.6	<0.001
PFR/PER	1.09 ± .25	0.87 ± .31‡	1.13 ± .35	<0.001
Time to peak filling rate (ms)	150 ± 18	189 ± 43§	170 ± 29§	<0.005
Contribution of atrial systole*				
% of EDV	10 ± 4	23 ± 13§	13 ± 7	<0.001
% of SV	17 ± 6	30 ± 17§	16 ± 9	<0.001
Regional LV asynchrony				
Variation among 20 sectors				
Time to minimal volume (ms)	19 ± 6	34 ± 15	24 ± 10	<0.001
Variation among four quadrants				
Time to peak ejection rate (ms)	13 ± 4	18 ± 12†	16 ± 12	NS
Time to minimal volume (ms)	10 ± 6	25 ± 19	15 ± 4‡	<0.005
Time to peak filling rate (ms)	12 ± 6	35 ± 24	21 ± 16	<0.001
Regional filling during atrial systole*				
Variation among 20 sectors (% of EDV)	6 ± 1	11 ± 4	10 ± 4	<0.05
Variation among four quadrants (% of EDV)	7 ± 4	10 ± 6†	7 ± 3	<0.001

*Measured in patients with distinct diastasis interval (25 normal subjects and 44 patients with hypertrophic cardiomyopathy). Statistical difference compared with normal subjects: †p <0.05; ‡p <0.01; §p <0.001. Data are mean ± SD. EDV = end-diastolic volume; HCM = hypertrophic cardiomyopathy; LV = left ventricular; PFR/PER = peak filling rate/peak ejection rate ratio; SV = stroke volume.

cardiomyopathy was associated with greater regional heterogeneity in the magnitude of rapid diastolic filling compared with normal, manifested by greater variation in the contribution of atrial systole to regional end-diastolic volume by both sector and quadrant analysis (Table 1, Fig. 1 and 2). A weak but significant correlation was observed between the regional variation in contribution of atrial systole and global peak filling rate ($r = 0.41$, $p < 0.01$).

Localization of asynchronous regions. The regional variation in contribution of atrial systole was analyzed on

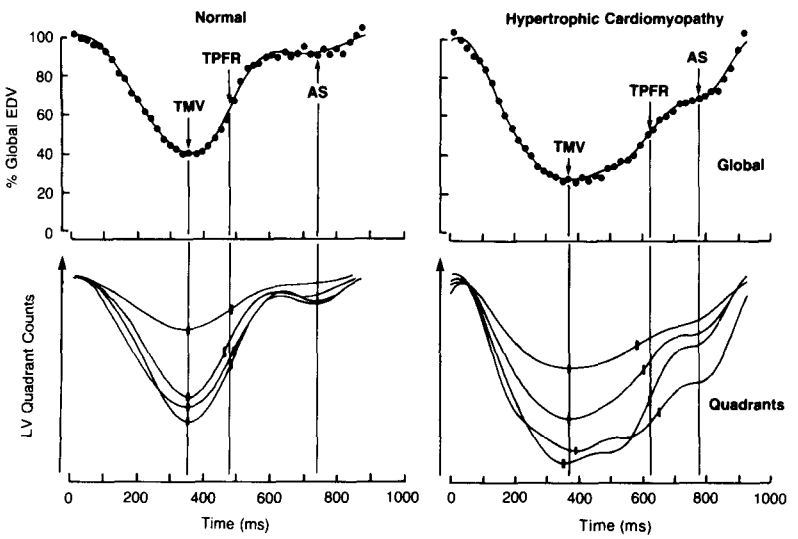

Figure 1. Global (**top**) and quadrant (**bottom**) time-activity curves in a normal subject and a patient with hypertrophic cardiomyopathy. The global data demonstrate reduced rate and extent of rapid filling, prolonged time to peak filling rate and increased contribution of atrial systole (AS) in the patient with hypertrophic cardiomyopathy. **Vertical lines** indicate global time to minimal volume (TMV) and time to peak filling rate (TPFR), and **short vertical bars** indicate these times in each quadrant curve. Systolic and diastolic synchrony are evident in the normal subject, whereas the patient with hypertrophic cardiomyopathy manifests diastolic asynchrony and regional variation in the relative magnitude of rapid filling and atrial systole. EDV = end-diastolic volume; LV = left ventricular.

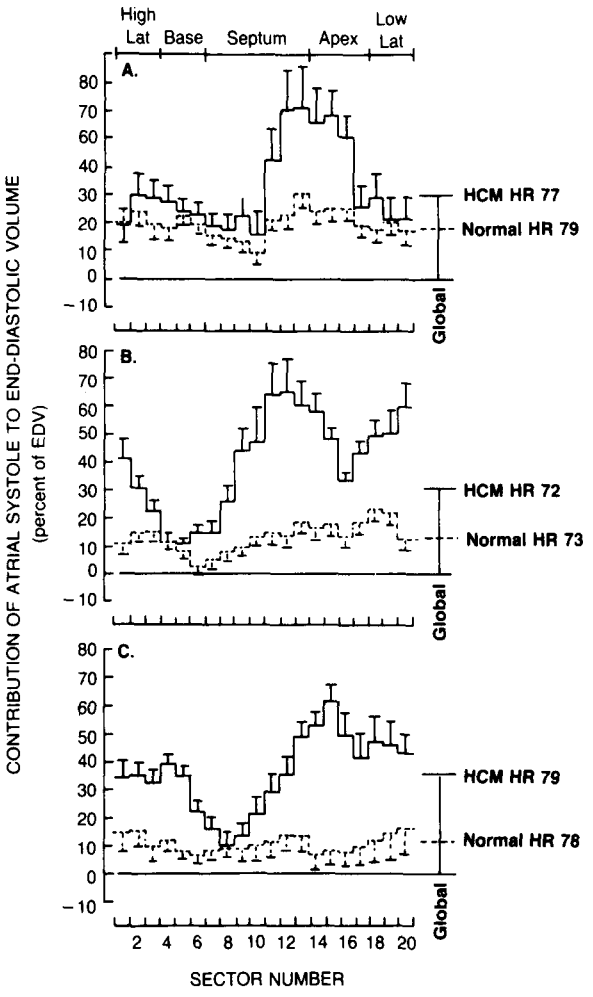

Figure 2. Contribution of atrial systole to end-diastolic volume for each of 20 sectors in three patients (**A, B** and **C**) with hypertrophic cardiomyopathy (HCM) compared with normal subjects of matched heart rate (HR). The contributions of atrial systole to global end-diastolic volume are shown in the **right** portion of each panel. Lat = lateral.

a sector by sector basis for each patient (Fig. 2). In each study, regions with accentuated contribution of atrial systole compared with other regions of the left ventricle were assessed qualitatively and tabulated. Sectors with augmented filling during atrial systole were localized to the ventricular septum or to the septum and left ventricular apex in 14 patients (Fig. 2A), involved both the septum and posterolateral wall in 24 (Fig. 2B) and were confined to the lateral wall in 3. In the remaining seven patients, there was apparently homogeneous regional filling in that no localized region of increased contribution of atrial systole could be identified.

Of the 33 patients in whom two-dimensional echocardiographic and radionuclide angiographic correlations were available, the localization of regions with accentuated filling during atrial systole corresponded to the distribution of left ventricular hypertrophy in 18 patients. Among the other 15 patients, in whom regional radionuclide angiographic and echocardiographic data were discordant, the radionuclide angiographic results in 11 patients indicated accentuated filling during atrial systole in severely hypertrophied regions but also in regions of the left ventricle that did not appear to be substantially hypertrophied by echocardiography.

Effect of verapamil. Verapamil did not affect indexes of global left ventricular systolic function (Table 1): ejection fraction, peak ejection rate and time to minimal volume were not altered during drug therapy. Despite a significant decrease in heart rate, indexes of global rapid diastolic filling improved during verapamil therapy, as previously described (5,6,27): peak filling rate increased and the magnitude of filling during atrial systole decreased, reflecting an increase in the contribution of rapid filling to global left ventricular diastolic and stroke volumes. Verapamil also reduced the severity of regional systolic and diastolic asynchrony (Table

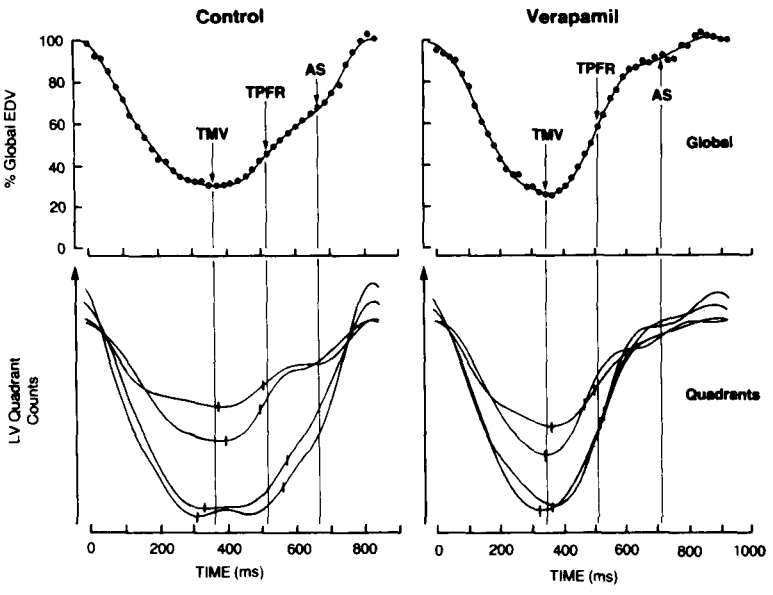

Figure 3. Variation among quadrants in time to minimal volume (TMV) and time to peak filling rate (TPFR) before (Control) and after verapamil therapy in a patient with hypertrophic cardiomyopathy. Reduction in diastolic asynchrony after verapamil, with greater homogeneity in the relative magnitude of rapid filling and atrial systole (AS), is associated with improved global rapid diastolic filling. Other abbreviations as in Figure 1.

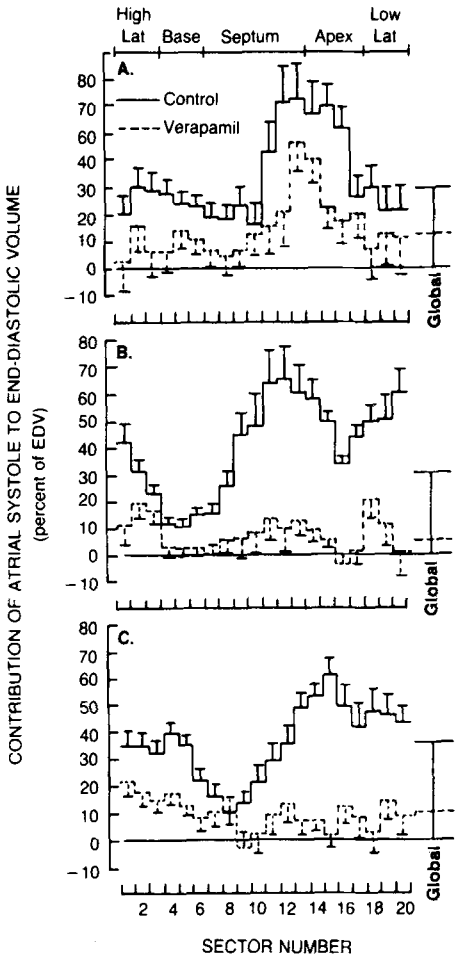

Figure 4. Contribution of atrial systole to end-diastolic volume plotted as a function of sector number before (Control) and during verapamil therapy in the same three patients illustrated in Figure 3 (**A, B,** and **C**). Filling during atrial systole is more homogeneous among sectors after verapamil. The contribution of atrial systole to global end-diastolic volume, shown in the **right** portion of each panel, is reduced by verapamil.

1, Fig. 3) and decreased the regional variation in filling during atrial systole (Fig. 3 and 4), reflecting greater homogeneity in the relative contribution of rapid diastolic filling. Although the magnitude of decrease in the regional variation in filling volume during atrial systole by both sector analysis and quadrant analysis was small (1 and 3%, respectively) and did not exceed the reproducibility limits of these measurements, the mean decrease in regional variation in time to minimal volume of 10 ms approached the reproducibility limit of this measurement (11 ms), and the mean decrease in variation in time to peak filling rate of 14 ms exceeded its reproducibility limit (12 ms). Among the 48 patients, the decrease in regional asynchrony was greater than the reproducibility limit in 21 patients for variation in time to minimal volume and in 23 patients for variation in time to peak filling rate. Verapamil effects on global diastolic filling and regional nonuniformity were not related to the presence or severity of an outflow tract gradient.

Discussion

Regional functional nonuniformity in hypertrophic cardiomyopathy. Left ventricular relaxation and filling are impaired in many patients with hypertrophic cardiomyopathy (1–6,12,13), and altered left ventricular diastolic function contributes importantly to the clinical manifestations of the disease (27,40). Reduced rate and magnitude of rapid diastolic filling arise from factors determining the passive elastic properties of the left ventricle (7–11), such as hypertrophy, fibrosis and cellular disorganization, and also from factors affecting the dynamics of left ventricular relaxation. Relaxation may be impaired in hypertrophic cardiomyopathy on the basis of both inactivation-dependent and load-dependent processes (41,42). Inactivation-dependent mechanisms include ischemia (43,44) or possibly other primary processes resulting in intracellular calcium ion overload, whereas load-dependent mechanisms might include (among others) alterations in extent of fiber shortening (41), reduced rate and extent of coronary blood flow (43,44) and reduced wall tension at the onset of mitral valve opening (42). Regional asynchrony or nonuniformity is another load-dependent mechanism affecting global left ventricular relaxation (42), in which persistent interaction of contractile elements into diastole leads to regional myocardial tension prolongation, resulting in prolonged or incomplete (or incoordinate) ventricular relaxation. Previous models of myocardial ischemia and clinical studies of coronary artery disease (14–24) have demonstrated the important influence of temporal inhomogeneity throughout the left ventricle on global abnormalities of ventricular relaxation and filling. Regional asynchrony has been identified in patients with hypertrophic cardiomyopathy (1,3) and such regional abnormalities have been implicated in the disturbances of global diastolic function (42). However, neither the relation between regional asynchrony and impaired left ventricular filling nor the potential reversibility of regional asynchrony in hypertrophic cardiomyopathy has been studied intensively.

In our investigation, we used radionuclide angiographic techniques to evaluate regional and global left ventricular function before and after verapamil therapy. Our data indicate that significant systolic and diastolic asynchrony is prevalent in patients with hypertrophic cardiomyopathy in the absence of coronary artery disease, and that regional diastolic asynchrony is related to regional variation in the relative contributions of rapid diastolic filling and atrial systole to end-diastolic volume. This regional variation in the timing and extent of rapid filling, in turn, relates to global disturbances in the rate, timing and magnitude of left ventricular filling. These data suggest that in many patients with hypertrophic cardiomyopathy, as in patients with coronary

artery disease, impaired global diastolic filling may result at least in part from regional nonuniformity of left ventricular systolic and diastolic function.

Factors contributing to regional nonuniformity. There are several possible mechanisms that might contribute to regional nonuniformity in hypertrophic cardiomyopathy. These include heterogeneous myocardial hypertrophy (and hence regional differences in wall stress during both systolic and diastolic phases of the cardiac cycle), regional foci of myocardial fibrosis, regional variation in the rate and extent of coronary blood flow and regional myocardial ischemia (or other primary processes resulting in intracellular calcium overload). It is not possible to identify with certainty the contributing factor or factors on the basis of the current noninvasive information. Despite this limitation, our results underscore the role of regional nonuniformity as a load-dependent determinant of left ventricular relaxation and filling (42). Our data also indicate that factors other than hypertrophy itself contribute to impaired regional diastolic function, because one-third of patients manifested reduced rapid filling in segments of the left ventricle that were not greatly hypertrophied. These data support previous observations in hypertrophic cardiomyopathy of diastolic abnormalities in left ventricular regions of normal wall thickness (45) and suggest either that the cardiomyopathic process may exist in the absence of substantial hypertrophy, or that excessive wall stress in regions without hypertrophy may compromise myocardial function in these regions.

Effect of verapamil. Improvement in indexes of regional left ventricular asynchrony and diastolic inhomogeneity during verapamil therapy suggest that dynamic, reversible mechanisms, rather than fixed regional morphologic abnormalities, must be responsible at least in part for regional nonuniformity in hypertrophic cardiomyopathy. Verapamil efficacy in this context might reflect improved regional relaxation stemming from salutary alterations in loading conditions of the hypertrophied left ventricle, such as reduced end-systolic pressure and increased end-diastolic volume (with no increase in end-diastolic pressure) (46–48). Alternatively, verapamil has the potential to increase regional coronary blood flow, which could act as a load-dependent mechanism to potentiate the relaxation process (41). In addition to these possible load-dependent effects, verapamil may also enhance myocardial inactivation by reduction of intracellular calcium overload (either by direct mechanisms or indirectly by amelioration of ischemia).

Reduction in regional diastolic nonuniformity during verapamil treatment was associated with enhanced global rapid diastolic filling: the peak rate and extent of rapid filling increased and the time to peak filling rate decreased. Previous data indicate that these changes in global diastolic filling are clinically relevant and correlate with lessening of symptoms and objective improvement in exercise tolerance during treatment with verapamil (27).

Conclusions. Our data demonstrate that asynchronous and nonuniform regional systolic and diastolic function in patients with hypertrophic cardiomyopathy, as in patients with coronary artery disease, may contribute importantly to impaired global left ventricular diastolic filling. The dynamic rather than fixed nature of these regional abnormalities suggests that left ventricular nonuniformity does not arise purely from irreversible alterations in left ventricular regional morphology, but may also reflect potentially reversible regional variation in myocardial inactivation or load. Although the precise mechanism responsible for regional nonuniformity and its modulation by verapamil cannot be determined from our data, our findings provide evidence that the beneficial effects of verapamil on global left ventricular diastolic function in hypertrophic cardiomyopathy may be mediated by reduction in regional asynchrony.

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